

MEETING OVERVIEW:
"CANCER PHARMACOLOGY IN INFANTS AND YOUNG CHILDREN"

A workshop sponsored by the National Cancer Institute-Cancer Therapy Evaluation Program was held in Washington, D.C. on May 9th, 2003, to discuss the current approach to dosing of chemotherapy drugs in infants and young children. The workshop developed from a survey of COG protocols indicating that the dosing instructions for a variety of standard chemotherapy drugs in infants and young children differed by disease committee without clear reason. Workshop participants included pediatric pharmacologists with expertise in the developmental changes that affect drug disposition and pediatric pharmacologists involved in oncology drug development. Pediatric oncologists from disease committees for cancers occurring in this younger patient population also participated. The workshop included an educational session on pharmacology and pharmacokinetic principles applicable to infants and young children. Participants discussed the guidelines currently used for dosing chemotherapy, the reasons for the current dosing parameters, and whether a more rational, evidence-based approach to dosing chemotherapy drugs in infants and young children could be established.

The chemotherapy dosing guidelines for cancers affecting the youngest children typically adjust chemotherapy drug dosing to accommodate infants and toddlers. However, there is little published information for pediatric oncologists to draw from when constructing chemotherapy-dosing recommendations in the creation of treatment regimens affecting young children. The "rule of 30", which allows the conversion of a BSA drug dose from mg/m² to mg/kg, appears to be a pharmacology concept that all pediatric oncologists have encountered and readily apply. Individual disease committees apply the "rule of 30" for children <12 months, children <3 years, or by weight (<10 kg, <12 kg, <30 kg). Additionally, some committees further decrease the dosing of chemotherapy agents by 50% for infants <12 months of age. The effect of these various dosing approaches is to dramatically adjust the comparative dose of a chemotherapy agent given to infants and young children treated on the same protocol; and the administered dose can change drastically as a child crosses an age or weight boundary during a multiple course chemotherapy regimen. While the goal of this individualized dosing is to reduce variability in the drug effect, both the anti-tumor effect and toxic effect, the varied application of drug dosing recommendations for the same drug in different regimens has very little supporting rationale.

Historically, the drug dosing guidelines used in treatment trials have been based on acceptable toxicities and not on targeting tumor or serum drug levels. It is apparent that many of the current dosing guidelines were developed due to drug-related toxicity experienced in earlier clinical studies, and pharmacologic information in children is limited.

Principles of pediatric pharmacology were discussed in order to understand important concepts affecting pediatric chemotherapy dosing. A consistent theme among the presentations of drug disposition was the lack of correlation between data from adults, adolescents and older children and data from infants and young children. The factors of drug absorption, metabolism, distribution, and elimination are all affected by the age and physiologic maturity of the child. It is known that the infant develops functional drug metabolism pathways, according to isoform-specific patterns, that control drug biotransformation. During this maturational change, shunting of drug metabolites can occur with the potential for age-specific differences in drug toxicity and effect. Drug distribution for young children is affected by the changes in body water, gradual increases in drug-protein binding, increases in adipose tissue mass, and changes in the compartmental distribution of the drug in the body. The significant changes in renal function, especially GFR, with increasing age influences drug pharmacokinetics and the child's clinical response to a drug. It is difficult to predict renal function in children, and studies of individual drugs are necessary. Studies of carboplatin have demonstrated no significant shift in PK for infants, suggesting that regimen-required decreases in dosing may result in underexposure to carboplatin in young patients. Importantly, for newer oral drugs, the developmental gut changes may affect drug absorption characteristics during the first 36 months of life. Absorption characteristics and gastrointestinal bioavailability established in older children and adults cannot be extrapolated to infants and young children.

Information regarding specific chemotherapy agents was reviewed. Of importance is the significantly greater incidence among infants and young children of neurotoxicity for vincristine, hepatic toxicity for actinomycin D and ototoxicity for cisplatin. There is also information suggesting that very young patients may be more severely affected by anthracycline-related cardiac toxicity and mucositis and ifosfamide-related nephrotoxicity and rickets. For virtually all of these older agents and the newer camptothecin agents, the limited available data indicate that weight-based dosing in young children normalizes the drug clearance profiles and may improve the toxicity profiles, bringing these profiles in line with that of older children. Exactly when to apply the weight-based dosing for each agent remains unclear.

Implicit in the discussions of drug dosing and the limited pharmacokinetic information available is the notion that drug dose can serve as a marker for drug exposure in these regimens; even though drug dose is not a direct predictor of drug exposure. For pediatric oncology, the optimal drug exposure has traditionally been sought in the context of acceptable toxicity; however, these optimal drug exposures have not been quantified. Toxicity has been the basis for past dose-reduction studies, and, for certain tumors such as Wilms, outcome remained good despite the decrease in drug dose, although the drug exposure remains unknown. Further, multiple agents with overlapping toxicities and anti-tumor efficacies are used in the chemotherapy regimens, limiting the value that single-agent drug exposure information could provide. Finally, pediatric phase 1 studies suggest that the relationship of drug dose and drug exposure is so variable that a small or large change in drug dose may have an unpredictable impact on drug exposure.

To improve the dosing recommendations for commonly used drugs, participants proposed including pharmacokinetic studies in phase 3 treatment studies, which accrue the majority of the infants and young children. This approach may also be necessary for future agents, as phase 1 studies typically accrue patients of the median patient age of 11 or 12 years, with very few patients accrued under age 3 or 4 years. Rather than using sample intensive pharmacokinetic approaches typical of phase 1 studies, the use of population pharmacokinetics was proposed as a means to obtain data from many subjects, but requiring few samples per patient. This approach estimates a population average and variance for pharmacokinetic parameters using sparse sampling data sets and may be adaptable to the large phase 3 studies conducted by the COG.

The action items from the meeting included:

1. Establishing a list of commonly used chemotherapy agents for which pharmacokinetic data would provide useful information.
2. Defining the type of pharmacokinetic data that would be needed to derive the useful information.
3. Defining the pharmacokinetic methodology and logistical approaches necessary to obtain the pharmacokinetic data.
4. Organizing a common approach to conducting the pharmacokinetic studies within the framework of phase 3 studies among different disease committees.
5. Considering the use of a nomogram for transitioning drug dosing parameters across the affected age or weight range to reduce the dramatic shift in calculated dose for individual patients.
6. Working with disease committees to determine the appropriateness and historical data supporting the dosing parameters currently in place.

It is hoped that the pursuit of this pharmacokinetic data will provide a better understanding of each agent's role within multi-agent regimens. This information could facilitate the incorporation or substitution of other agents into the regimens in the future. This information can also allow the incorporation of pharmacologically guided drug dosing and pharmacogenetic dose modification in future chemotherapy trials.

The transcript of the workshop, including the available slide presentations, will be posted on the Cancer Therapy Evaluation Program website (<http://ctep.info.nih.gov/resources/index.html>) in the next month.